REMARKS

Objections to the specification

Amendments to the specification have been made to correct certain informalities objected to by the Examiner. The amendments do not add new matter and entry of same is respectfully requested.

The Claims

Claims 1-20 and 22-44 are currently pending in the application and Claims 1-20 and 22-25 have been cancelled without prejudice as directed to a non-elected invention. Claims 26-44 are currently pending in the application.

Rejections under 35 U.S.C. 112

Claims 26-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The Examiner argues that the exact meaning of the phrase "modifying sensitivity to cell cycle-specific chemotherapeutic agents" is unclear. In particular, the Examiner argues that it is unclear what the term "modifying" is meant to encompass or what is being modified. It is also argued that it is unclear what compounds are encompassed by the term "cell-cycle specific chemotherapeutic agents".

Claim 26 in its present form recites "modifying the sensitivity of cells containing human stem cell factor receptors to a chemotherapeutic agent … " In addition, the term "sensitivity" has, as one of its meanings, "the ability of an organism or part of an organism to react to stimuli" [*The American College Dictionary*, Random House Inc. New York (1963)]. It is clear that the claim refers to the response for reaction of cells containing human stem cell factor receptors to the effects of a chemotherapeutic agent as the subject matter being modified by the claimed method.

The term "modify" is also clear to one skilled in the art. As one of its meanings, the term "modify" indicates "to

change somewhat the form or qualities thereof; alter somewhat" [*The American College Dictionary*, Random House Inc. New York (1963)]. This definition of the term "modify" does not specify whether an increase or a decrease has occurred, but merely states that some change or alteration has happened. The term is not indefinite merely because it does not specify an increase or a decrease. To the contrary, it is clear that "modify" can encompass both. Applicants maintain that one skilled in the art would understand the meaning of the term "modify".

Applicants maintain that the term "cell-cycle specific chemotherapeutic agents" is clear to one skilled in the art for the reasons set forth in the Response and Amendment dated May 6, 2002. However, without acquiescing to the rejection and solely to advance prosecution, Applicants have amended Claim 26 to recite "chemotherapeutic agents". It is believed that the compounds encompassed by the term "chemotherapeutic agents" are clear to one skilled in the art.

Claims 26-44 are rejected under 35 U.S.C. 112, first paragraph, as the specification allegedly does not enable one skilled in the art to which it pertains to make and/or use the invention.

The Examiner alleges that Claim 26 is not enabled because the specification allegedly fails to teach how to perform the method and complete method steps, and the specification does not provide working examples wherein all of the steps required to practice the method are employed.

The Examiner also alleges that the antibodies used to carry out the claimed method are not enabled because: (1) the specification allegedly does not enable the epitope to which the antibody produced from the hybridoma cell line ATCC No. HB 10716 binds; and (2) the specification allegedly has not demonstrated the reproducible production of antibodies which have properties identical to that produced by the hybridoma cell line ATCC No. HB 10716, or antibodies which bind to a human stem cell factor receptor and have the claimed properties.

Applicants disagree for the following reasons and maintain that the subject matter of the claims is enabled by the disclosure.

The method of Claim 26 may be practiced without undue experimentation using the specification and the knowledge of one skilled in the art.

The method of Claim 26 recites the step of administering a monoclonal antibody or fragment thereof in an amount sufficient to inhibit binding of stem cell factor to a stem cell factor receptor or to decrease the growth or development of receptor-containing cells, thereby modifying the sensitivity of the cells to a chemotherapeutic agent. Applicants have provided a working example of an antibody (termed SR-1 and produced by the hybridoma cell line ATCC No. HB 10716) which when administered inhibits binding of SCF to its receptor and decreases the growth of receptor-containing cells. Examples 1 and 2 describe the production of the SR-1 antibody and Examples 4, 5 and 6 disclose the inhibition of SCF binding and decrease in cell growth exhibited by the SR-1 antibody. These examples may be used to generate additional antibodies which bind to a stem cell growth factor receptor, and the antibodies may be further tested for inhibition of SCF binding and decrease in cell growth by following the procedures set forth in the specification.

It would not require undue experimentation to identify the amounts of an antibody needed to modify the sensitivity of receptor-containing cells to chemotherapeutic agents, since the responses of such cells to chemotherapeutic agents were well known and could be readily assayed using available procedures. Moreover, the Examiner acknowledges at p. 9 of the Office Action that " ... administration of the antibody would not be undue ... ". No more than routine experimentation would have been required to carry out the invention.

The Examiner has not established a *prima facie* case of nonenablment with respect to the claimed antibodies.

In order to establish a *prima facie* case of nonenablement, the PTO must set forth a reasonable explanation as to why it believes that the scope of protection being sought is not adequately enabled by the specification *In re Wright* 27 USPQ2d 1510 (Fed. Cir. 1993). The Examiner's alleges that the isolation of the SR-1 antibody exemplified in the application was "fortuitous" and not reproducible, and that it would be unpredictable to find any other examples of an antibody having the same characteristics. One apparent reason for this conclusion is that only a single antibody is exemplified in the application. Applicants are not aware of any basis in law which states that the number of examples in an application is *prima facie* evidence of nonenablement. The Examiner has not offered any scientific or legal basis to assert that the claimed antibodies would be unpredictable and could not be made reproducibly. Instead, what is offered is mere speculation that many possible antibody variable regions would need to be screened to find an antibody with the claimed properties and this effort would require undue experimentation. However, the Examiner has not pointed to anything in the disclosure that would suggest any difficulty in obtaining the presently claimed antibodies using the teachings of the specification.

Moreover, the argument that screening many antibody variable regions constitutes undue experimentation contradicts current case law. The Federal Circuit has determined that screening of antibodies for a desired property is considered to be within the level of skill in the art:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

In re Wands 8 USPQ 2d 1406 (Fed. Cir. 1988)

It is clear that no "reasonable doubt" as to the reproducibility of the claimed antibodies has been established. There is no basis to allege that undue experimentation would be required to obtain an antibody which binds to a receptor recognized by a human stem cell factor and exhibits the properties set forth in the application. The argument for undue experimentation based on the need to screen many antibodies is clearly inconsistent with Federal Circuit case law. Merely alleging lack of enablement with no reasoning or evidence to support it is not sufficient to shift the burden of proof to Applicants.

The claimed antibodies are enabled in view of the claims in U.S. Patent No. 5,919,911.

A claim in an issued U.S. patent is presumed to have satisfied the requirements of 35 U.S.C. 112 including the provision that the specification enables the subject matter encompassed by the claim. Applicants wish to point out the following claims in U.S. Patent No. 5,919,911 (hereafter the '911 patent).

Claim 1 of the '911 patent reads as follows:

> A monoclonal antibody, or a fragment thereof, which binds to an epitope on a receptor recognized by human stem cell factor, said epitope being recognized by the monoclonal antibody produced by the hybridoma cell line ATCC No. HB 10716.

Claim 5 of the '911 patent reads as follows:

> A monclonal antibody, or fragment thereof, which specifically binds to a receptor recognized by human stem cell factor in a manner that inhibits binding of human stem cell factor to said receptor by at least 50%.

Claim 8 of the '911 patent reads as follows:

> A monclonal antibody, or fragment thereof, which specifically binds to a receptor recognized by human stem cell factor in a manner that decreases the growth rate of receptor-containing cells in the presence of human stem cell factor by at least one half.

The '911 patent claims priority from U.S. Serial No. 07/681,245, the same application from which the present application claims priority.

In summary, Claims 1, 5 and 8 (and claims depending therefrom) of the '911 patent recite a monoclonal antibody or fragment which binds to a receptor recognized by human SCF and (1) binds to an epitope recognized by the monoclonal antibody from ATCC HB 10716; or (2) inhibits binding of human SCF to its receptor by at least 50%; or (3) decreases the growth rate of receptor-containing cells by at least one half. These antibodies are also recited in Claims 26-44 of the present application.

The presumption of enablement enjoyed by the claims of the '911 patent means, among other things, that the claimed antibodies can in fact be obtained reproducibly and without undue experimentation, that the epitope of the antibody produced by the hybridoma cell line no. ATCC HB10716 is enabled, and that one may obtain other antibodies having the properties set forth in the claims. In the face of clear evidence of enablement, the Examiner has inexplicably taken a completely opposite view. Applicants maintain that the rejection should be withdrawn.

It is also argued that the subject matter of Claim 27 is not enabled as it would require undue experimentation to practice the invention with other antibodies which bind to an epitope recognized by the antibody produced by the hybridoma cell line ATCC No. HB 10716. The arguments set forth above are applicable to this rejection as well. The Examiner cites Greenspan et al. (Nature Biotech. 7, 936-937 (1999)) to support the contention that defining epitopes "is not as easy as it

seems". However, the Greenspan reference merely cautions one skilled in the art not to rely solely on a mutational analysis (such as alanine scanning mutagenesis) to determine those amino acid residues that comprise an epitope. There is nothing in the reference to suggest that determining an epitope on a protein would require undue experimentation

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for reciting "essentially entirely". The Examiner alleges it is unclear whether the antibody inhibits binding or not. Applicants maintain that the phrase "essentially entirely" is clear to one skilled in the art based on the plain meaning of the term and how it is used in the specification. The term "entirely" is defined as "wholly, fully or completely" [*The American College Dictionary*, Random House Inc. New York (1963)]. Moreover, the term is used in the specification on p. 21, line 12 where it is stated that:

> Preferably the inhibition will decrease binding of SCF to its receptor by at least 50%, more preferably by at least 75%, more preferably by at least 90%, and most preferably inhibition will decrease binding of SCF to its receptor *essentially entirely*. [italics added]

It is clear that the term "essentially entirely" refers to a decrease in binding of SCF to its receptor that is for all practical purposes complete. For example, when binding of SCF to its receptor in the presence of an antibody is below detectable levels, it can be said that the antibody inhibits binding essentially entirely. It is maintained that the term is clear to one skilled in the art and the rejection should be withdrawn.

Claims 27 and 28 are rejected under 35 U.S.C. 112, first paragraph, as the specifically allegedly does not provide evidence that the claimed biological materials are (1) known and readily available to the public; and (2) reproducible from the written description. It was requested that evidence of a deposit

with the American Type Culture Collection of the hybridoma cell line having accession number HB 10716 be provided.

Applicant provide herewith a copy of the certificate of biological deposit with the American Type Culture Collection (presently located in Manassas, VA). It is requested that the rejection be withdrawn.

CONCLUSION

Claims 26-44 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

Robert B. Winter
Attorney/Agent for Applicant(s)
Registration No.: 34,458
Phone: (805) 447-2425
Date: March 10, 2003

Please send all future correspondence to:

U.S. Patent Operations/ RBW
Dept. 4300, M/S 27-4-A
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

VERSION SHOWING CHANGES

In the specification:

At p. 1, line 1, please insert the following paragraph:

(new) The invention described herein was made in the course of work under grant no. DK31232 from the National Institutes of Health and JFRA 217 from the American Cancer Society. The United States Government has certain rights in this invention.

This application is a divisional of U.S. Serial No. 08/255,193 filed June 7, 1994, now U.S. Patent No. 5,922,847, which is a divisional of U.S. Serial No. 08/011,078 filed January 29, 1993, now U.S. Patent No. 5,489,516, which is a continuation of U.S. Serial No. 07/681,245 filed April 5, 1991, now abandoned.

At p. 1, replace the paragraph at lines 10-17 with the following:

Stem Cell Factor (SCF) is a growth factor that stimulates the proliferation of pluripotent hematopoietic progenitor cells. It has been produced recombinantly in *E. coli* and various mammalian cells [Zsebo et al., *Cell* 63:195-212 (1990); and co-pending U.S. Patent Applications 07/589,701, 07/573,616, and 07/537,198, filed October 1, 1990, August 24, 1990, and June 11, 1990, respectively, now abandoned.]

At p. 12, replace the paragraph at lines 14-25 with the following:

Stem Cell Factors (SCFs) useful in these assays include any of the SCFs from various species. Such SCFs are usually in solution with a suitable adjuvant, which adjuvant, may contain buffers, salts, etc. Preferably, the SCF will be human SCF (HuSCF), more preferably a recombinant human SCF (rHuSCF), and most preferably a rHuSCF produced in *E. coli*. Such SCFs can be obtained as previously described [Zsebo et al., *Cell* 63:195-212 (1990); and co-pending U.S. Patent applications 07/589,701,

07/573,616, and 07/537,198, filed October 1, 1990, August 24, 1990, and June 11, 1990, respectively, now abandoned, all of which are hereby incorporated by reference for their relevant teachings].

At page 24, replace the paragraph at lines 3-26 with the following:

Appropriate antigens for use in sensitization were any cell displaying SCF receptors. The presence of SCF receptors was determined using radiolabelled SCF. Human and rodent $SCF^{164-165}$ was obtained according to the methods of Zsebo et al., *Cell* 63:195-212 (1990); and copending U.S. Patent Applications 07/589,701, 07/573,616, and 07/537,198, filed October 1, 1990, August 24, 1990, and June 11, 1990, respectively, now abandoned. These SCFs were labelled with ^{125}I using the chloramine-T method of Hunter and Greenwood [*Nature* 194:495-496 (1962)]. The specific activity of the ^{125}I human SCF (hSCF) varied from 2,000 to 2,500 Ci/mmol. Both ^{125}I hSCF and ^{125}I rat SCF (rSCF) ratained the ability to bind to SCF-receptor-containing cells. Moreover, self displacement analysis [Calvo et al., *Biochem. J.* 212:259-264 (1983)] with ^{125}IhSCF and unlabelled hSCF demonstrated that the binding affinity was not altered by iodination. A number of other hematopoietic growth factors were tested for binding to the erythroleukemia cell line OCIM1 [Papayannopoulou et al., *Blood* 72:1029-1038 (1988)]. Table 1 shows that a 100-fold molar excess of unlabelled hSCF competed very effectively for binding, while a variety of other growth factors did not.

At p. 31, line 21 through p. 32. line 10, replace the paragraph with the following:

Five days following the third injection, the spleen was removed and splenic cells were fused with NS-1 murine meyloma cells [Nowinski et al., *Virology* 93:111-126 (1979)]. The supernatants from a total of 288 hybridoma wells were screened for the ability to block binding of ^{125}IhSCF to OCIM1 cells as

described in Example 5, below. A positive hybridoma was identified, cloned and grown as an ascites-producing tumor in pristane-primed Balb/C mice. The antibody was identified as IgG2a and was named SR-1 (deposited as BA7.3C.9 with the American Type Culture Collection, Rockville, Maryland USA on April 4, 1991 and given the ATCC Accession Number HB 10716. Screening of additional hybridomas should lead to the identification of additional anti-SCF receptor monoclonal antibodies at a similar frequency.

In the claims:

26. (amended) A method of modifying the sensitivity of ~~a~~ cells containing ~~a~~ stem cell factor receptors to a ~~cell cycle specific~~ chemotherapeutic agent comprising administering a monoclonal antibody, or fragment thereof, which binds to an epitope on a receptor recognized by human stem cell factor, in an amount sufficient to inhibit binding of stem cell factor to the receptor or to decrease the growth or development of receptor-containing cells, thereby modifying the sensitivity of the cells to the ~~a cell cycle specific~~ chemotherapeutic agent.